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Fast oxidation of secondary alcohols by the bromate-bromide system using cyclic microwave heating in acidic water

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ABSTRACT

We report an improved, gentle, cyclic microwave activation technique for the oxidation of secondary alcohols using nonhazardous hypobromous acid (BrOH) as the reagent in acidic water. Several aliphatic and aromatic secondary alcohols were successfully oxidized to the corresponding ketones using this technique in high yields and with only minor amounts of side products.

Microwave irradiation is a very rapid method for heating a reaction mixture containing polar or ionic components as well as being a modern tool in green chemistry. There has been growing interest in microwave heating since 1986, when pioneering investigations were performed.[1–4] Microwave irradiation is an alternative compared to conventional heating and has been widely applied in synthesis and reported in numerous reviews.[5–10] Among solvent-free reactions, microwave heating has become popular, because the heating effect is directed toward the reagents.[4,11,12] It has several advantages compared to conventional heating: the reaction mixture can be smoothly and homogenously heated, the energy is transferred directly to the components instead of to the reaction flask, the solvent can be used to regulate the efficiency of the heating,[5] and requires shorter reaction times compared to conventional reactions. Microwave activation often leads to a cleaner reaction with a better yield and selectivity.[13,14]

Water is an ideal solvent for microwave-activated reactions.[15] It also fulfills several of the requirements of green synthesis: it is nontoxic, nonflammable, abundant, and inexpensive.[8,16,17]

Recently, we developed a benign and simple oxidation of secondary alcohols at room temperature using a nonhazardous mixture of NaBr (2 equiv) and $NaBrO_3$ (1 equiv) in acidic water.[18] The oxidizing species which forms under these reaction conditions is hypobromous acid as reported earlier.[19–23]

$$BrO_3^- + 2Br^- + 3H^+ \rightarrow 3BrOH \tag{1}$$

At room temperature these oxidations took several hours.[24] In this Letter we report a cyclic microwave activation technique developed for this oxidation which led to a significant reduction in reaction time, increased yields, and a decrease in the amount of side products.

In the oxidation of 2-butanol (**1**) to 2-butanone (**2**) using the bromide-bromate reagent in acidic water, the active oxidant, BrOH, is in equilibrium with molecular bromine (Eq. 2). This can be seen as a reddish vapor above the reaction mixture.

$$BrOH + HBr \rightleftharpoons Br_2 + H_2O \tag{2}$$

During initial microwave-activated experiments, it was noticed that the oxidation reactions were sensitive to temperature. The formation of side products increased with an increase in reaction temperature. It was believed that irradiation at a low power would activate the reaction mixture more gently and shorten the reaction time. A cyclic microwave heating technique was developed for this purpose.[25] The reaction mixture is repeatedly heated and cooled in short cycles as set in the heating program, by using the lowest irradiation power. A typical heating diagram of this technique is presented in Figure 1a.

Microwave reactors have a minimum temperature below which the temperature cannot be set. Often this temperature is 60 °C, which restricts the use of this cyclic heating technique. For comparison a typical heating diagram for conventional microwave heating is shown in Figure 1b.[26]

In cyclic heating the irradiation power is pulsed in cycles of 20 s (Fig. 1c) which generates a sine-type temperature curve wherein the temperature varies in the range of 33–35 °C. A similar cyclic irradiation technique was used in the oxidation reactions with a

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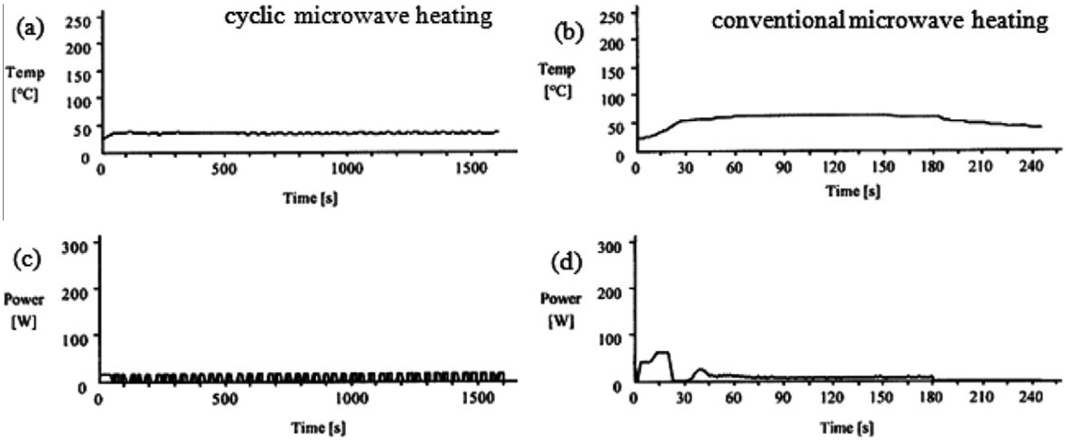
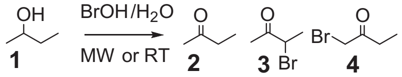


Figure 1. A typical heating (a) and power (c) diagram for cyclic microwave heating at 33–35 °C: programmed heating (irradiation of 20 s at a power of 15 W) and cooling (20 s or 10 s) stages altered in cycles. For comparison a typical heating (b) and power (d) diagram for conventional microwave heating at 60 °C is presented.

Table 1

Effect of reaction time, concentration and temperature on the product distribution in the oxidation of 2-butanol (**1**) with 1.05 equiv of BrOH



Entry	Concentration of **1**	Temperature (°C)	Irradiation power (W)	Reaction time (min)	Unreacted starting compound (%)	Products[a,b] (%)		
					1	**2**	**3**	**4**
1	0.4	rt	–	120	21	76	3	–
2	0.4	33–35	15	10	9	91	–	–
3	0.4	48–50	15	10	7	85	6	2
4	0.4	60	70 to 10	5	9	78	10	3
5	0.2	rt	–	120	17	79	4	–
6	0.2	33–35	15	17	23	75	2	–
7	0.2	33–35	15	30	2	96	2	–
8	0.2	48–50	20	10	17	79	4	–
9	0.2	60	70 to 10	5	–	89	9	2
10	0.2	60	70 to 10	10	–	81	14	5

[a] Reaction procedure. A mixture (2.5 mL) of NaBr (2 equiv) and $NaBrO_3$ (1 equiv) in an acidic solution (H_2SO_4, 3 equiv of H^+) was added to a microwave tube containing 2-butanol (1 mmol).[28]

[b] The product distribution was analyzed by GC–MS.[29]

slight increase in the power to keep the reaction temperature in the range of 48–50 °C.[27] In conventional microwave heating, the temperature is automatically regulated to 60 °C using high irradiation power (max. 70 W) and is then maintained with a low power (ca. 10 W) (Fig. 1d).

The oxidation of 2-butanol (**1**) using microwave irradiation produced, in addition to 2-butanone (**2**), the brominated compounds 3-bromo-2-butanone (**3**) and 1-bromo-2-butanone (**4**) (Table 1). To support the oxidation and simultaneously avoid the formation of these undesired bromo compounds, the effect of the concentration, reaction temperature, and total reaction time on the product distribution was studied.

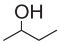
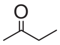
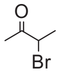
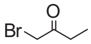
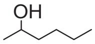
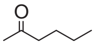
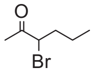
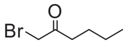
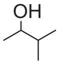
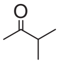
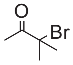
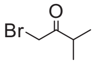
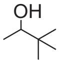
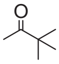
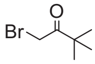
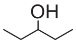
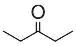
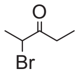
The results in Table 1 show an obvious interdependence between the temperature and the formation of side products. At a low temperature, the yield of 3-bromo-2-butanone (**3**) was low and the formation of 1-bromo-2-butanone (**4**) could be totally avoided (Table 1, entries 1, 2, 5–7). By comparison, the usual microwave-assisted reaction at 60 °C produced 10% of 3-bromo-2-butanone (**3**) and 3% of 1-bromo-2-butanone (**4**) (Table 1, entry 4).

The low concentration of 2-butanol (0.2 mol/L) combined with the low reaction temperature caused a decrease in the formation of side products (Table 1, entries 5–8). Cyclic microwave heating in the temperature range 48–50 °C with a low concentration of 2-butanol (**1**) reduced the amount of side products **3** and **4** (Table 1, entry 3 vs entry 8). During microwave activation at 60 °C a similar reduction in the formation of side products was not detected as the concentration of **1** was decreased (Table 1, entry 4 vs entry 9). Table 1, entry 7 shows that by using cyclic heating in the temperature range 33–35 °C for 30 min, 2-butanol (**1**) is nearly completely oxidized to 2-butanone (**2**).

Pre-prepared BrOH contained some molecular bromine (Eq. 2), which disturbed the reproducibility of the oxidation.[30] In subsequent oxidations the active BrOH was generated in situ by adding the acid in one portion to the reaction mixture just before sealing the reactor tube.[31] The reaction mixture was heated for various reaction times and temperatures. Samples from the reaction mixtures were analyzed by GC–MS, and the results of the oxidation of several aliphatic alcohols are presented in Table 2 and those of aromatic alcohols in Table 3.

Table 2 shows that heating using the cyclic microwave technique accelerated the reaction but did not enhance the amounts of side products. To obtain a high yield in the oxidation, the correct reaction time is important. If the reaction time is too long the ketone starts to brominate and unwanted side products are obtained. The use of low power cyclic microwave heating at 33–35 °C allows

Table 2
Oxidation of aliphatic secondary alcohols using cyclic microwave heating with variable reaction times and temperatures

Entry	Time (min)	Temperature (°C)	Irradiation power (W)	Alcohol (%)	Product mixture[a,b] (%)		
					Ketone	Brominated side products	
1							
	360	rt[c]	–	–	100	–	–
	25	33–35	15	–	100	–	–
	35	33–35	15	–	98	2	–
	50	33–35	15	–	93	7	–
	5	60	70 to 10	–	93	6	1
	10	60	70 to 10	–	89	10	1
2							
	135	rt[c]	–	–	96	3	1
	25	33–35	15	4	92	4	–
	40	33–35	15	2	90	6	2
	5	60	70 to 10	4	∼92	4	Trace
	10	60	70 to 10	–	76	18	6
3							
	240	rt[c]	–	8	91	1	–
	10	33–35	15	17	>82	<1	–
	20	33–35	15	11	∼87	2	Trace
	40	33–35	15	8	89	2	1
	3	60	70 to 10	2	97	1	–
	5	60	70 to 10	–	96	4	–
4							
	180	rt[c]	–	–	97	3	
	15	33–35	15	4	96	–	
	30	33–35	15	3	97	–	
	45	33–35	15	2	92	6	
	3	60	70 to 10	17	78	5	
	5	60	70 to 10	2	92	6	
5							
	210	rt[c]	–	5	90	5	
	20	33–35	15	1	98	1	
	30	33–35	15	–	96	4	
	40	33–35	15	–	91	9	
	3	60	70 to 10	15	85	–	
	5	60	70 to 10	14	80	6	

[a] Reaction procedure: 2-butanol (1 mmol) and a mixture of NaBr (2 equiv): $NaBrO_3$ (1 equiv) were added to a microwave reactor tube and 10% acid (H_2SO_4, 3 equiv of H^+) was added.[31]

[b] The product distribution was analyzed by GC–MS.[29]

[c] Room temperature reactions (not microwave); the acid was added over 135 min.[18]

a longer heating time compared to conventional microwave heating at high power and at 60 °C, without the formation of brominated compounds. For example, in Table 2, entry 4, oxidation with cyclic microwave heating (33–35 °C) for 45 min and conventional microwave heating at 60 °C for 5 minutes, both produced 6% of the brominated product.

The results of the oxidation of aromatic alcohols using the cyclic microwave heating technique were encouraging (Table 3). Compared to the use of the conventional microwave heating the amount of side products was reduced. The reaction at 60 °C yielded brominated products (Table 3, entries 3 and 4), which were not detected in the oxidation at room temperature or by using cyclic microwave heating at 33–35 °C.

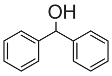
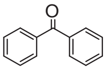
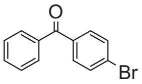
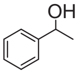
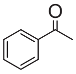
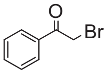
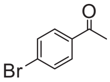
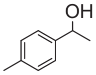
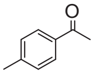
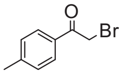
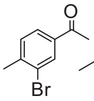
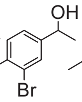
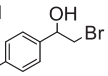
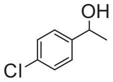
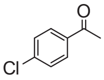
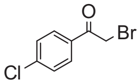
The oxidation reaction was sensitive even to mild temperatures. The cyclic heating technique, however, accelerated the reaction without the formation of side products. For aliphatic alcohols the reaction conversion was 88–100% using cyclic microwave heating at 33–35 °C (Table 2). The reaction time varied in the range of 15–40 min and the reaction rate was faster than at room temperature.

Oxidation of aromatic alcohols was highly sensitive to heating (Table 3, entries 2 and 3), but with the delicate cyclic microwave heating the formation of side products was negligible. With aromatic alcohols cyclic microwave heating at 33–35 °C produced nearly complete oxidation in a time range of 10–15 min.

This oxidation procedure is simple and does not require any pre-treatments and the reagents can be used as received without the use of an inert atmosphere. The oxidation proceeds rapidly and cleanly in acidic water without any additional catalyst or organic solvent.

We have shown that the cyclic microwave heating technique is a more suitable activation method compared to conventional microwave heating in the oxidation of secondary alcohols by aqueous BrOH. It is a benign, gentle, and simple procedure with several benefits including shorter reaction times, provides high yields, and produces only small amounts of side products.

Table 3
Oxidation of aromatic secondary alcohols using cyclic microwave heating with variable reaction times and temperatures

Entry	Time (min)	Temperature (°C)	Irradiation power (W)	Alcohol (%)	Reaction products (%)[a,b]				
					Product	Brominated side products			
1									
	135[c]	rt	—	—	100	—			
	10	33–35	15	6	94	—			
	30	33–35	15	3	93	4			
	5	60	70 to 10	5	95	—			
	10	60	70 to 10	2	97	1			
2									
	135	rt[c]	—	—	>99	Trace	Trace		
	10	33–35	15	—	~100	Trace	—		
	20	33–35	15	—	~98	2	Trace		
	40	33–35	15	—	~98	2	Trace		
	3	60	70 to 10	—	94	—	6		
	5	60	70 to 10	—	85	7	8		
3									
	135	rt[c]	—	—	95	2	2	1	—
	5	33–35	15	17	81	—	2	—	—
	10	33–35	15	—	97	—	3	—	—
	15	33–35	15	—	>92	<1	4	3	—
	3	60	70 to 10	18	49	7	6	1	19
	5	60	70 to 10	—	68	8	8	—	16
4									
	135	rt[c]	—	—	100	—			
	5	33–35	15	17	83	—			
	10	33–35	15	12	88	—			
	15	33–35	15	6	94	—			
	5	60	70 to 10	3	97	—			
	10	60	70 to 10	—	98	2			

[a] Reaction procedure: 2-butanol (1 mmol) and a mixture of NaBr (2 equiv): $NaBrO_3$ (1 equiv) were added to a microwave reactor tube and 10% acid (H_2SO_4, 3 equiv of H^+) was added.[31]

[b] The product distribution was analyzed by GC–MS.[29]

[c] Room temperature reactions (not microwave); the acid was added over 135 min.[18]

We believe that this new heating technique should be amenable to other reactions which are sensitive to side reactions or increased reaction temperatures.

Acknowledgment

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Supplementary data

Supplementary data (NMR spectra and ESI-TOF or ES-MS spectral characterization of the ketone products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.009.

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24. The room temperature oxidation required 1.05 equiv of active BrOH as a dilute aqueous solution prepared from a bromide-bromate mixture (2:1, respectively) with 10% H_2SO_4.
25. To keep the reaction temperature mild, the heating was cycled. Even continuous heating at the lowest power (15 W) gave a temperature that was too high for sensitive reagents.
26. The microwave-assisted synthesis was performed using a SmithCreator microwave reactor with a single-mode cavity in closed vials. The lowest set temperature of the microwave reactor was 60 °C.
27. To reach the reaction temperature, the initial heating took some time. Compressed air cooling (0.06 MPa) used during the heating affected the temperature. The heating programs used for different reaction temperatures and volumes are as follows:

    Reaction volume 2.5 mL: 33–35 °C; heating for 30 s (15 W) and cooling for 60 s. 48–50 °C; heating for 40 s (15 W), cooling for 10 s, heating for 30 s (15 W) and cooling for 10 s.

    Reaction volume 5.0 mL: 33–35 °C; heating for 20 s (15 W), cooling for 20 s, heating for 20 s (15 W) and cooling for 10 s. 48–50 °C; heating for 40 s (20 W), cooling for 10 s, heating for 30 s (20 W) and cooling for 10 s.
28. *CAUTION*: In preliminary experiments the pre-prepared, active BrOH reagent should be handled and used in a well-ventilated fume hood. The active reagent produces toxic Br_2 vapor.

    A typical procedure using the active pre-prepared BrOH reagent: To a solution of 2-butanol (0.092 mL, 1 mmol) in a microwave tube were added 1.05 equiv (2.5 mL) of a solution containing a 2:1 ratio of NaBr (0.072 g, 0.70 mmol) and $NaBrO_3$ (0.053 g, 0.35 mmol) with H_2SO_4 (0.53 mmol). The tube was heated using the microwave reactor for the appropriate amount of time, or it was left at room temperature.
29. EI mass spectra (GC–MS) were recorded at 70 eV using a HP 5973 mass spectrometer and a HP 6890 series GC system with a DB-624 column.
30. Br_2, which equilibrates with BrOH (Eq. 2), vaporized in air and decreased the amount of active BrOH. This means that when the reagent is pre-prepared and several portions of active BrOH taken, the final portions include relatively small amounts of active reagent compared to the first portions.
31. A typical oxidation procedure used for various secondary alcohols: Into a microwave reactor tube with alcohol (1 mmol) in H_2O (4 mL) was added 0.5 mL of a solution of NaBr (0.072 g, 0.70 mmol) and $NaBrO_3$ (0.053 g, 0.35 mmol). 10% H_2SO_4 (0.5 mL, 0.53 mmol) was added in one portion.